IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	**Stuart Newman**		
Application Serial No.:	**08/993,564**	**Examiner:**	**D. Crouch**
Filed:	**December 18, 1997**	**Art Unit:**	**1633**
For:	**Chimeric Embryos and Animals Containing Human Cells**		
Attorney Docket #:	**45010-00601**		

SUPPLEMENTAL RESPONSE

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Applicant files this Supplemental Response to the Office Action dated August 7, 2000. The Examiner rejected Applicant's claims under 35 USC §101, §102(b), §103, and §112, as discussed below. Applicant timely filed a fully responsive Amendment and Response on February 7, 2001, but to date has not received any further communication from the Patent and Trademark Office ("PTO"). Applicant respectfully submits that the February 7, 2001 Amendment and Response places the application in condition for allowance.

Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55-71 were present in this application. By Applicant's February 7, 2001 Amendment and Response Claims 1, 3, 4, 6, 7, 10, 13, 28, 30, 31, 33, 34, 39-43, 53, 59, and 70 were amended, Claims 2, 5, 16, 29, 32, 44-48, and 56-58 were canceled without prejudice, and new Claims 72-92 were added. The application as originally drafted and subsequently amended claims various

permutations of a chimeric embryo. More specifically, claims are drawn to chimeric embryos, and cell lines and animals isolated or originating from chimeric embryos. The Examiner has rejected the claims on five separate grounds:

- First, the Examiner has rejected Claims 1-7, 13, 16, 28-34, 39-48, and 56-71 under 35 U.S.C. § 101 as being directed to non-statutory subject matter, namely as falling within an exception to statutory subject matter as "embracing a human being."
- Second, the Examiner has rejected Claims 10, 13, 16, 28, 29, 32-34, 50, and 66-71 under 35 U.S.C. § 102(b) as being anticipated by certain references disclosing the introduction of human hematopoietic cells into mice *in utero* and mouse primordial germ cells and human fetal and embryo cell lines, and humans in which baboon organs were transplanted.
- Third, the Examiner has rejected Claims 1, 2, 5, 16, 28, 29, 32-34, 38-48, 56, 57, and 59-65 under 35 U.S.C. § 103(a) as being obvious, in view of a reference disclosing sheep/goat chimeras and chimeric sheep/goat pregnancies.
- Fourth, the Examiner has rejected all claims under 35 U.S.C. § 112, first paragraph, based on the assertion that the specification would not enable one of ordinary skill in the art to practice the invention, citing unpredictable outcomes in chimera formation, and the lack of a structural definition of the chimeric embryo.

- Fifth, the Examiner has rejected all claims under 35 U.S.C. § 112, second paragraph as being vague and indefinite as to what would be considered a chimeric embryo.

The subject matter of the appended claims is made by the intervention of man. The claimed subject matter is not naturally occurring and constitutes patentable subject matter under 35 U.S.C. §101. The vast array of references cited by the Examiner establishes the level of background knowledge of persons of ordinary skill in the art. In the context of that knowledge, the specification satisfies the requirements of 35 U.S.C. §112. The techniques that are needed to make and use the claimed invention are well within the ordinary level of skill in the art as evidenced by the multiple references identified by the Examiner in the Office Actions. In spite of the comprehensiveness of the art, no one has practiced, taught, or suggested the use of these well known and amply documented techniques to make the claimed invention. The Examiner has recognized the richness of the level of ordinary skill, yet, has identified no reference teaching or suggesting the claimed invention as a whole.

35 U.S.C. §101

Claims 1-7, 13, 16, 28-34, 39-48, and 56-71 were rejected under 35 U.S.C. §101 as directed to nonstatutory subject matter. The Examiner maintains the position that the pending claims encompass or "embrace" human beings. The Examiner maintains that absent express intent that Congress enacted §101 to cover human beings as eligible for patenting, such intent cannot be inferred. The Examiner states that an embryo with human cells, but for a small percentage, or perhaps of one cell type, is considered human.

The Examiner asserts that the PTO has rejected claims that encompass a human being under 35 U.S.C. §101, and requires that claims drawn to animals be expressly limited to "non-human" animals. Despite the lack of an express exception for human beings in §101, the Examiner asserts that a claim that encompasses a human being is drawn to non-statutory subject matter. Applicant maintains that the subject matter claimed in the present invention is not a human being and that no statutory authority supports the rejection on these grounds.

The rejection is improper for two reasons: (1) it is not a proper statutory requirement for patentability; and (2) the claimed subject matter is not a human being but rather, man-made chimeric cell lines, embryos and animals developing from them. Applicant respectfully submits that the Commissioner has no authority to reject the claims of the present invention--that are explicitly "made by man"--on the grounds that they "embrace a human being."

The statute does not restrict patentability of inventions based upon the invention "embracing a human being." The Examiner recognizes that the Court in *Chakrabarty* held that statutory subject matter shall "include anything under the sun that is made by man." *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). The claimed subject matter is not naturally occurring. It is not disputed by the Examiner that the claimed subject matter is "made by man." Applicant claims a chimeric embryo, a cell line, or chimeric animal derived from the chimeric embryo. A human being is not claimed.

Applicant respectfully submits that a proportion of human cells in an organism does not make that organism a human being. In addition, the original application, and subsequent amendments, do not include any claims to a human being, but only

contains claims to a chimeric embryo, a cell line, or a chimeric animal isolated or originating from the chimeric embryo. Applicant respectfully directs the Examiner to Applicant's remarks in its February 7, 2001 Response.

The fact that a chimeric embryo, a cell line, or a chimeric animal has a human cellular component cannot exclude it from patentability, any more than the many patents that share that feature and have been awarded by the PTO. Subject matter consisting of, or derived from, human cells in non-human animal systems has been, and continues to be, granted patents in the area of biotechnology.

35 U.S.C. § 102(b)

Claims 28, 29, and 32-34 are rejected under 35 U.S.C. §102(b) as being anticipated by Pixley et al. (1994) Pathobiol. **62**, 238-244. The Examiner asserts that the organisms disclosed by Pixley, et al., i.e. xenografts, xenotransplants, or even allografts or allotransplants, fall squarely into the definition of a "chimera". In addition, the Examiner contends that the disclosure of Pixley, et al. continues to anticipate the pending claims as the rejected claims include the scenario where the second animal species is mouse.

The Examiner states that the invention was anticipated by the description by Pixley et al. (1994) of the introduction of human hematopoietic cells into mice *in utero*. Pixley, J. S., Zanjani, E. D., Shaft, D. M., Porada, C., and Mackintosh, F. R. (1998). Prolonged Hematopoietic Chimerism in Normal Mice Transplanted *in utero* with Human Hematopoietic Stem Cells. *Pathobiology* **66,** 230-9) conducted late embryo grafting experiments to produce hematopoietic organisms, i.e., mixtures of blood forming cells in an organism (mouse) that is unambiguously of one species. Applicant respectfully

directs the Examiner's attention to the amendments and remarks filed in Applicant's February 7, 2001 Response.

Applicant has amended the claims to the use of embryonic cells in the formation of the chimeric embryo, cell line, and chimeric animals. The chimeric embryo of the present invention is not intended to include fetal stage xenografts or any entity constructed with cells of developmental stages later than the inner cell mass.

The claims were amended to limit the Applicant's invention to the use of human and non-human primate cells. The present invention and amended claims describe chimeric embryos containing human and non-human primate cells, where aggregation of embryonic cells (i.e., blastomere cells, blostocyst cells, undifferentiated immortal cells, pluripotent cells, totipotent cells, and embryonic stem cells) of two or more species is performed. This is entirely different, and leads to different developmental outcomes, than the engraftment of **multipotent** stem cells during fetal stages as described by Pixley et al.

Claims 10, 50, and 68 are rejected under 35 U.S.C. §102(b) as being anticipated by the Catalog of Cell Lines and Hybridomas, 7th ed., American Type Culture Collection (ATCC), Rockville, MD. 20852-1776, 1992, entry HTB 157, HTB 158, and HTB 160, page 271, and cell line CRL2378. The Examiner states that the existence of human cell lines in the American Type Culture Collection anticipates the present invention.

Claims 10 and 68 are rejected under 35 U.S.C. §102(b) as anticipated by ATCC entries HTB 157, 158, and 160, p. 271. The Examiner maintains that any

immunological differences exhibited by cells derived from chimeras would depend upon the cell type.

Claims 10, 50, and 68 are rejected under 35 U.S.C. §102(b) as being anticipated by ATCC, entry CRL-2378, designated MA-104. The Examiner contends that the breadth of Applicant's claims would encompass a cell line isolated from embryonic kidney tissue of a Rhesus monkey, as cells isolated and used to generate a cell line may not include both species.

Cells derived from chimeras are known to differ in immunological properties from equivalent cells in non-chimeric animals. One of ordinary skill in the art would expect that this would also likely pertain to cell lines derived from chimeras. Applicant does not completely understand the PTO's continued rejection under 35 U.S.C. §102(b) as being anticipated by the American Type Culture Collection Catalogue of Cell Lines. Applicant directs the Examiner to the amendments and remarks submitted in Applicant's February 7, 2001 Response in which Applicant amended the claims to more accurately describe the embryonic cell types and immunological tolerance of the cell lines of the present invention.

Claims 13, 66, 67, and 69-71 are rejected under 35 U.S.C. §102(b) as being anticipated by Starzl et al. Starzl et al. disclose humans in which baboon kidneys or livers were transplanted and resulted in chimerism of the patient. The Examiner contends that the breadth of the claims encompass the organisms disclosed by Starzl et al., and, as such, the claims are rejected.

The human-animal chimeras disclosed by Starzl et al. are different from those of the present invention since they are the result of adult tissue cells of one species

colonizing adult tissues of another species, rather than the result of developmental cooperation of early embryonic cell types of different species. Applicant directs the Examiner to Applicant's amendments and remarks filed with the February 7, 2001 Response.

The human patients described by Starzl et al., who had received baboon hearts or livers, or chimpanzee kidneys *via* transplantation, were not reported to exhibit any morphological or phenotypic similarities to baboons or chimpanzees, indicating lack of synergistic development, nor did they exhibit any tissue level chimerism other than that due to leukocyte transfusion from the donor species. The animals of Starzl et al. are not considered to originate from the chimeric embryos as disclosed and claimed in the present invention. Applicant respectfully submits that Starzl et al. fails to disclose the subject matter of the claimed invention.

Claim 16 is rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over human or non-human primates as found in nature.

Claim 16 is directed to a descendant of the chimeric animal of Claim 13. The Examiner contends that the descendant of a chimeric animal is not necessarily any different from one of the source species.

The chimeras themselves would be expected to have endothelial cells with different gene expression profiles from either of the originating species, even though each endothelial cell is genetically one or the other species. It is reasonable to expect that this property of the endothelium would be propagated through the germline, leading to descendent organisms of one or the other species that have altered endothelial

properties. Applicant respectfully directs the Examiner to its Amendment and Response filed February 7, 2001, in which Claim 16 was canceled without prejudice.

35 U.S.C. §103

Claims 1, 2, 5, 28, 29, 32-34, 38-48, 56-57, and 59-65 are rejected under 35 U.S.C. §103 as being unpatentable over Gustafson et al. (1993) *J. Reprod. Fert.* **99**, 267-273. The Examiner contends that because Gustafson et al. discloses sheep-goat chimeras, the art itself in combination with Gustafson et al. would motivate one with ordinary skill in the art to make aggregates including human cells. The Examiner contends that motivation does not have to be found specifically in a prior art reference, but can be taken from the general state of the art itself.

Although this reference utilized chimeras to study pregnancy retention and placental development, i.e., some of the things that might be studied if chimeric animals containing human and nonhuman cells were available, as per an embodiment of the present invention, the issues and discussion are very far from anything involving human biology. This paper has been cited twice in the literature indexed in the Scientific Citations Index ("SCI") since the time it was published. Neither reflects the motivation attributed to Gustafson, et al., by the Examiner.

The present invention describes embryos produced from embryonic cells or ES cells from two different primate species, one of which is a human. This is entirely different from the disclosure of Gustafson et al., 1993. The paper of Gustafson et al., is solidly within the scientific field of animal husbandry, where the issue of hybridization is important, leading, for example, to mules. Investigators in this field might be motivated to apply Gustafson's teachings on sheep and goats to cattle, swine, horses, etc.

Because primates are not domesticated farm animals, readers of papers like Gustafson et al. would not be motivated to consider this group of animals as potential subjects of such investigations. Thus shifting consideration to primates represents one major displacement from the area of teaching of Gustafson. Secondly, one of the species in the invention is designated as human. But within the field of primate biology there is a teaching away, for cultural and social reasons, from consideration of overcoming reproductive barriers between nonhuman species and humans.

The Examiner has provided no reference that teaches or suggests chimeric embryos containing human cells. Examiner maintains the rejection based upon the ability of the embryo to form a cooperative entity. Applicant submits that there was actually a teaching away of the formation of chimeric embryos containing human cells. The only references relying upon Gustafson did so in the context of embryo mortality, not formation. As the references cited by the Examiner establish, the area of developmental biology is unpredictable, making the utility of the present invention so powerful. It is for this reason, among others, that the claimed subject matter is not obvious.

Applicant submits that it would not be obvious under Gustafson et al. for one of ordinary skill in the art at the time of the invention to make a cell aggregate comprising human cells.

35 U.S.C.§112

Applicant takes this opportunity to supplement its response to the 35 U.S.C. §112 rejection based upon two applications recently granted by the PTO, U.S. Patent Nos. 6,211,429 to Machaty et al. ("Machaty") and 6,376,743 to Yanagimachi ("Yanagimachi").

These patents, and more particularly, the references cited therein, support Applicant's position that the specification as filed in the present application provides an enabling disclosure for how to make and use the claimed invention under 35 U.S.C. §112.

Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55-71 were rejected under 35 U.S.C. §112, First Paragraph for lack of adequate enabling disclosure. The Examiner has taken the position that the specification fails to provide an enabling disclosure for how to make and use the claimed invention. Applicant respectfully submits that the claim amendments and remarks presented in its February 7, 2001 Response obviates the grounds for the rejection.

Claims 39-48 and 55 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner maintains that if a claim specifically recites a limitation on viability, the limitation must be disclosed in the specification. The fact that the specification states that the embryo can be propagated for varying periods, does not enable claims that recite a specific limitation, i.e., a specific time. Applicant respectfully directs the Examiner's attention to Applicant's Amendment and Response filed February 7, 2001.

Applicant, in the original specification, states "Once chimeric embryos are produced they can be propagated for varying periods of time in culture, where they may undergo a series of developmental steps . . . For some uses, the embryos can be brought to term, forming the chimeric animals of the invention." The claims were

amended to reflect this disclosure. Applicant respectfully submits that it is well known in the art that chimeric organisms may or may not cease to be viable at any given time.

In an effort to more clearly define the present invention, Applicant either amended or canceled the subject claims. The Examiner is directed to the February 7, 2001 Amendment and Response. Applicant amended Claims 39-43 to claim the chimeric embryo at a particular stage of development, and Claims 44-48 were canceled without prejudice.

Claims 56 and 57 were rejected under 35 U.S.C. §112, first paragraph. The Examiner contends that the specification does not disclose that the chimeric embryo would exhibit composite morphology or multi-tissue chimerism. The Examiner states that these limitations constitute new matter and that the specification does not provide adequate written description of the claimed invention.

Applicant respectfully submits that the description of a chimeric embryo as found in Gilbert's *Developmental Biology* (Sinauer, 1997): "the result of two or more early cleavage (usually 4- or 8-cell) embryos that have been artificially aggregated to form a composite embryo" (p. 187) and as being made from early stage embryo cells (blastomeres) and embryo stem (ES) cells (189), and as defined by Papaioannou and Gardner, as being made from early cleavage embryos and inner cell mass cells (Papaioannou, V., and Gardner, R. L. (1979). Investigation of the lethal yellow Ay/Ay embryo using mouse chimaeras. *J Embryol Exp Morphol* **52,** 153-63), obviates the ground for this rejection. In every case in the scientific literature in which chimeric embryos were made according to these specifications multi-tissue chimerism resulted. In every case in the literature in which dual species chimeric embryos were made

according to these specifications, composite morphology also resulted. It would therefore be evident to one of ordinary skill in the art that producing dual or multi-species chimeric embryos according to this commonly accepted definition would imply multi-tissue chimerism and composite morphology.

Applicant respectfully argues that those traits are inherent in the organisms of the present invention as described by Applicant in the specification. Nonetheless, Applicant canceled Claims 56 and 57 without prejudice.

Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55-71 were rejected under 35 USC §112, First Paragraph for lack of adequate enabling disclosure. The Examiner has taken the position that the specification fails to provide an enabling disclosure for how to make and use the claimed invention. Applicant respectfully submits that the claim amendments and remarks presented its February 7, 2001 Response obviate the grounds for the rejection. Applicant provides the additional comments below in support of its position.

The Examiner asserts that the specification does not disclose the essential features of the claimed chimeras and that the specification describes the chimeras as having an unspecified degree of chimerism. The Examiner continues that the specification does not disclose what contribution each species would make to the chimera and that the written description is insufficient to inform a skilled artisan that Applicant was in possession of the claimed invention as a whole at the time the application was filed. The Examiner contends that the specification contains no specific description of the ultimate structure, physical and anatomical, of the chimeras, and that the contribution that each species makes to the chimera is not set forth. The Examiner

maintains that the skilled artisan cannot envision the detailed structure of the encompassed chimeras, cell lines, or animals, and therefore conception is not achieved. The Examiner is directed to Applicant's remarks submitted in its February 7, 2001 Response.

It is clear from the literature that species that are much more dissimilar than human and chimp or human and gorilla cooperate to produce a coherent organism (Fehilly, C. B., Willadsen, S. M., and Tucker, E. M. (1984). Interspecific chimaerism between sheep and goat. *Nature* **307,** 634-6; Meinecke-Tillmann, S., and Meinecke, B. (1984). Experimental chimaeras--removal of reproductive barrier between sheep and goat. *Nature* **307,** 637-8). Specifically, sheep and goats are biologically much more distant from one another (Randi, E., Fusco, G., Lorenzini, R., Toso, S., and Tosi, G. 1991. Allozyme divergence and phylogenetic relationships among Capra, Ovis and Rupicapra (Artyodactyla, Bovidae). *Heredity* **67,** 281-6) than human and chimpanzee (Takahata, N., and Satta, Y. 1997. Evolution of the primate lineage leading to modern humans: phylogenetic and demographic inferences from DNA sequences. *Proc Natl Acad Sci U S A* **94,** 4811-5). The chimpanzee has been known from the early 1980 to be an excellent model system for in vitro fertilization and early embryogenesis in humans because of the extensive similarities in early embryogenesis in these species (Gould, K. G. (1983). Ovum recovery and in vitro fertilization in the chimpanzee. *Fertil Steril* **40,** 378-83). One skilled in the art would fully expect that embryo chimeras constructed from human blastomeres, inner cell mass cells, or ES cells and chimpanzee or gorilla blastomeres, inner cell mass cells, or ES cells would have at least as the

degree of multitissue chimerism and composite morphology as that reported for sheep and goat.

Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55-71 were rejected under 35 U.S.C. §112, first paragraph for failing to teach how to make and use the invention. The Examiner does not agree with Applicant's statement that the technology for producing chimeric mammalian embryos is "robust". The Examiner contends that only a very few species have been used in making chimeric embryos, and that none of the prior art methods enable one to culture primate embryos. The Examiner maintains that it is unpredictable as to whether the culture methods used in mouse, rat, sheep, or goats could be extrapolated to primate embryos. Though one of skill in the art could easily mix together embryonic cells of two species, the formation of a cooperative entity and its viability for any length of time is completely unpredictable. Therefore, the Examiner maintains that the specification does not enable how to make the claimed embryos, cell lines, or animals.

The techniques for manipulating mammalian embryos are clearly robust and enabling for the production of chimeras. For example Hammer states in a 1998 retrospective (Hammer, R. E. (1998). Egg culture: the foundation. *Int J Dev Biol* **42,** 833-9):

> In 1963, Ralph [Brinster] reported a method for culturing eggs in microdrops of medium under oil (Brinster, 1963), which has become universally used. Two years later, he identified pyruvate as the central and essential energy source for early stages of mouse eggs (Brinster, 1965b). These two developments revolutionized in vitro studies of mammalian eggs and issued in an era of intense research activity concerning egg culture and egg manipulation. Effective formulations of culture media could now be developed to allow routine in vitro maintenance of eggs, and

> important parameters for these recipes were soon determined **Thus, a foundation of understanding about the biology of early mammalian eggs was established between 1960 and 1970, and subsequent studies have broadened this understanding.** However, the greatest impact of a simple, reliable egg culture method has been to provide the ability to perform complicated manipulative procedures on preimplantation stages of mammalian embryos. In no area has this been more important than in development of transgenic animals. All methods for generating germ line genetic modifications rely on the ability to maintain and manipulate eggs and early developmental stages in vitro without loss of developmental competence. The importance of efficient egg culture to manipulation and transgenesis is fundamental and **enabling**. [Emphasis added].

An earlier report (Anderson, G. B. (1985). Manipulation of the mammalian embryo. *J Anim Sci* **61,** 1-13).shows that by the early 1980s the robustness of mammalian embryo manipulation techniques and their transferability across species lines was already part of the practice of the field:

> Technological advances in manipulation of mammalian embryos outside the maternal environment have resulted in opportunities for study of preimplantation embryo development, identification of developmental phenomena that are unique to mammals, and further improvement of technology. Mammalian embryos may be cultured in vitro at 37 C for up to several days or they may be stored at -196 C indefinitely. The mammalian embryo possesses the unique capacity to regulate its development and differentiate into a normal individual after being stimulated to incorporate foreign cells or after a portion of its cells are removed. **This regulatory ability has proven useful in research dealing with the production of chimeras□Some of these manipulations have been carried out primarily in laboratory mice, but as animal scientists identify beneficial uses in farm animals, these procedures are being extended to embryos of the large domestic species.** [Emphasis added].

The Examiner contends that only a very few species have been used in making chimeric embryos. Applicant respectfully submits that this is not the case: Picard, L., Chartrain, I., King, W. A., and Betteridge, K. J. (1990). Production of chimeric bovine embryos and calves by aggregation of inner cell masses with morulae. *Mol Reprod Dev* **27,** 295-304; Onishi, A., Takeda, K., Komatsu, M., Akita, T., and Kojima, T. (1994). Production of chimeric pigs and the analysis of chimerism using mitochondrial deoxyribonucleic acid as a cell marker. *Biol Reprod* **51,** 1069-75; Schoonjans, L., Albright, G. M., Li, J. L., Collen, D., and Moreadith, R. W. (1996). Pluripotential rabbit embryonic stem (ES) cells are capable of forming overt coat color chimeras following injection into blastocysts. *Mol Reprod Dev* **45,** 439-43; Sumantri, C., Boediono, A., Ooe, M., Saha, S., and Suzuki, T. (1997). Fertility of sperm from a tetraparental chimeric bull. *Anim Reprod Sci* **46,** 35-45.

There is also evidence for intrauterine chimerism in the human, i.e., formation of a single individual from aggregation of blastomeres of fraternal twins: De la Chapelle, A., Schroder, J., Rantanen, P., Thomasson, B., Niemi, M., Tiilikainen, A., Sanger, R., and Robson, E. B. (1974). Early fusion of two human embryos? *Ann Hum Genet* **38,** 63-75; Mayr, W. R., Pausch, V., and Schnedl, W. (1979). Human chimera detectable only by investigation of her progeny. *Nature* **277,** 210-1.

The Examiner also states that none of the prior art enables one of ordinary skill in the art to culture primate embryos. Applicant respectfully submits that this is not the case: Pope, C. E., Pope, V. Z., and Beck, L. R. (1982). Development of baboon preimplantation embryos to post-implantation stages in vitro. *Biol Reprod* **27,** 915-23; Gould, K. G. (1983). Ovum recovery and in vitro fertilization in the chimpanzee. *Fertil*

Steril **40,** 378-83; Pope, V. Z., Pope, C. E., and Beck, L. R. (1984). SP-I secretion by baboon embryos in vitro. *Placenta* **5,** 403-12; Fourie, F. R., Snyman, E., and van der Merwe, J. V. (1987). Supplementation of Ham's F10 culture medium with three different sera in the culturing of baboon oocytes. *Comp Biochem Physiol A* **87,** 1103-6 and Pope, C. E., Dresser, B. L., Chin, N. W., Liu, J. H., Loskutoff, N. M., Behnke, E. J., Brown, C., McRae, M. A., Sinoway, C. E., Campbell, M. K., Cameron, K. N., Owens, O. M., Johnson, C. A., Evans, R. R., and Cedars, M. I. (1997). Birth of a western lowland gorilla (Gorilla gorilla gorilla) following in vitro fertilization and embryo transfer. *Am J Primatol* **41,** 247-60 all report the culture of primate embryos.

Machaty and Yanagimachi claim methods of obtaining or producing mammalian embryos, respectively. The disclosures, and references cited therein, enable one of ordinary skill in the art to culture primate embryos. Homa, S.T., et al. (1994). *Hum Reprod* **9**, 2356-2361; Herbert, M. (1995). *Hum Reprod* **10**, 2183-2186. Various methods are also disclosed for fusing and/or cooperatively aggregating two cell types together. Prather, R. (1996). *Proc Soc Exp Biol Med* **212**, 38-43; Prather, et al. (1991). *Animal Applications of Research in Mammalian Development*, R.A. Pedersen, et al., Eds., The Cold Spring Harbor Laboratory Press, 205-232. The various methods to culture primate embryos would have been well known to one of ordinary skill in the art. Chan, A.W.S. et al. (2000). Foreign DNA transmission by ICSI: injection of spermatozoa bound with exogenous DNA results in embryonic GFP expression and live Rhesus monkey births. *Mol Hum. Reprod.* **6**, 26-33; Bavister, B.D., Boatman, D.E., Leibfried, L. et al. (1983). Fertilization and cleavage of rhesus monkey oocytes *in vitro*. *Biol. Reprod.*, **28**, 983-999; Boatman, D.E. (1987) *In vitro* growth of non-human primate pre- and peri-

implantation embryos. In Bavister, B.D. (ed.), *The Mammalian Preimplantation Embryo*. Plenum Press, pp. 273-308; Lanzendorf, S.E., Zelinski-Wooten, M.B., Stouffer, R.L.,et al. (1990). Maturity at collection and the development potential of rhesus monkey oocytes. *Biol. Reprod.*, **42**, 703-711.

Applicant's specification describes three specific technologies for making interspecific embryo chimeras, with citations to the published literature. The Examiner has cited dozens of references, establishing that the techniques are not only well known in the published literature, but readily apprehended and used by researchers in the art for a wide variety of investigations.

All early mammalian embryos, including human embryos, undergo the same initial developmental steps. All go through a *two cell*, *four cell*, and *eight cell* stage, and all are initially surrounded by an extracellular layer known the *zona pellucida*. All form a hollow *blastula*, containing an *inner cell mass*. The inner cell mass further develops into two or more layers of cells known as the germinal layers. The germinal layers, the ectoderm, the mesoderm, and the endoderm, give rise to the various cell types that make up the adult animal. (An Introduction to Embryology, Fourth Edition (1975), Balinsky, B.I., W.B. Saunders Company, Philadelphia PA; Molecular Biology of the Cell, Second Edition (1989), Alberts, B. et al., Garland Publishing, Inc., New York, NY). Applicant respectfully submits that methods to create chimeric embryos were adequately disclosed and enabled the present invention.

The Examiner maintains that intraspecies chimeras of mouse/rat and sheep/goat cannot be extrapolated to human/non-human primate chimeras. The Examiner states that although human/chimp or human/gorilla may share greater than 90 percent DNA

homology (actually 98% DNA homology); however, the DNA homology does not account for anatomical differences, differences in gestation, or more importantly how to get a host mother to carry such a chimera. Applicant respectfully contends that the existing art was sufficient at the time of filing to permit one of ordinary skill in the art to construct the chimeric embyros, cell lines, and animals of the present invention.

Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55-71 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicant respectfully submits that the claim amendments and remarks presented its February 7, 2001 Response obviate the grounds for the rejection. Applicant provides the additional comments below in support of its position.

The Examiner contends that the phrase "chimeric embryo" renders the claims indefinite because it does not clear when a cell aggregation becomes an embryo, and that the specification does not set forth a definition of when a cell aggregation actually is considered an embryo. The Examiner interprets the term to mean simply a mixture of cells from two individuals.

By "viable embryo," Applicant is referring to a chimeric embryo which is alive (in the sense of respiration and not necessarily progressing full term) and capable of developing to the next or successive stage of development, as the term "viable embryo" is used in the developmental and reproductive biology literature. The subject claims were amended to more accurately describe that the embryonic cells must cooperate in order to form a viable embryo. It is evident from Machaty, Yanagimachi, and the references cited therein, that the definition of an "embryo" is well known to one of ordinary skill in the art.

Conclusion

While each application is evaluated on its own facts, Applicant respectfully submits that the PTO must provide a consistent interpretation as to what is patentable subject matter and what is not. Inventors routinely consult issued patents for guidance in determining the patentability of their own inventions. Applicant respectfully requests that the Examiner reconsider the pending claims, withdraw the rejections, and allow the claims in view of the February 7, 2001 Response and the additional information submitted in this Response.

Applicant respectfully submits that the claims define statutory subject matter that is patentable over the art of record and the application is in condition for allowance. Should the Examiner believe anything further is desirable to place the application in better condition for allowance, the Examiner is invited to contact Applicant's undersigned attorney at the telephone number listed below.

Respectfully Submitted,

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